ADAR1 promotes malignant progenitor reprogramming in chronic myeloid leukemia.

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Public Summary:
The molecular drivers of human progenitor reprogramming into self-renewing leukemia stem cells (LSC) has remained elusive. Although DNA sequencing has uncovered gene mutations that promote abnormal RNA processing and leukemic transformation, gene product diversity also may be generated by RNA editing mediated by adenosine deaminase acting on RNA (ADAR) enzymes that regulate stem cell maintenance. In this study, RNA-sequencing studies reveal high levels of expression of inflammatory mediators in human blast crisis CML progenitors and in BCR-ABL transduced normal cord blood stem cells. Moreover, expression of the inflammation-responsive form of ADAR1 (p150) correlated with generation of an abnormally spliced GSK3β gene product that has been previously linked to LSC self-renewal. Together, we have demonstrated that ADAR1 drives hematopoietic cell fate by skewing cell differentiation – a trend which occurs during normal bone marrow aging – and promotes LSC self-renewal through alternative splicing of critical survival and self-renewal factors. Notably, inhibition of ADAR1 through genetic knockdown strategies reduced self-renewal capacity of CML LSC, and may have important applications in treatment of other disorders that transform to acute leukemia. Together these data provide a compelling rationale for developing ADAR1-based LSC detection and eradication strategies.

Scientific Abstract:
The molecular etiology of human progenitor reprogramming into self-renewing leukemia stem cells (LSC) has remained elusive. Although DNA sequencing has uncovered spliceosome gene mutations that promote alternative splicing and portend leukemic transformation, isoform diversity also may be generated by RNA editing mediated by adenosine deaminase acting on RNA (ADAR) enzymes that regulate stem cell maintenance. In this study, whole-transcriptome sequencing of normal, chronic phase, and serially transplantable blast crisis chronic myeloid leukemia (CML) progenitors revealed increased IFN-gamma pathway gene expression in concert with BCR-ABL amplification, enhanced expression of the IFN-responsive ADAR1 p150 isoform, and a propensity for increased adenosine-to-inosine RNA editing during CML progression. Lentiviral overexpression experiments demonstrate that ADAR1 p150 promotes expression of the myeloid transcription factor PU.1 and induces malignant reprogramming of myeloid progenitors. Moreover, enforced ADAR1 p150 expression was associated with production of a misspliced form of GSK3beta implicated in LSC self-renewal. Finally, functional serial transplantation and shRNA studies demonstrate that ADAR1 knockdown impaired in vivo self-renewal capacity of blast crisis CML progenitors. Together these data provide a compelling rationale for developing ADAR1-based LSC detection and eradication strategies.

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